REMARKS

As a preliminary matter, applicant would like to address the Examiner's assertion that claims 40-114 are pending in the application and that a complete reply to the final rejection must include cancellation of the nonelected claims. On this matter, applicant respectfully notes that claims 40-114 were in fact canceled in the Amendment filed on January 6, 2003, and refer the Examiner to page 5 of the January 6, 2003, Amendment, specifically, to the first paragraph immediately under the heading "In the Claims" where the statement canceling the claims is set forth. In light of the foregoing, applicant respectfully requests the Examiner's acknowledgement that claims 40-114 were in fact canceled in the Amendment filed on January 6, 2003.

In the Office Action under reply, claims 3, 4, 16, 17, 216, 32-35 were withdrawn from consideration as drawn to a non-elected species and claims 1, 2, 5-15, 18-25, 27-31, and 36-39 were examined and subject to the following actions:

(1) Objection of claims 5 and 20 on formalities;

(2) Rejection of claims 1, 2, 5-15, 18-25, 27-31, and 36-39 under 35 U.S.C. § 1.112, second paragraph;

(3) Rejection of claims 1, 6, 18, 19, 23, and 24 under 35 U.S.C. § 102(e) as anticipated by Senapathy (U.S. Patent No. 6,521,428); and

(4) Rejection of claims 21 and 22 under 35 U.S.C. § 103(a) as obvious over Senapathy in view of Santamaria et al. (U.S. Patent No. 5,578,443).

Applicant acknowledges that the Examiner's rejections indicate that claims 2, 5, 7-15, 20, 25, 27-31, and 36-39 are free of art.

CLAIM OBJECTIONS:

Claims 5 and 20 stand objected to on formalities.

With respect to claim 5, applicant respectfully notes to the Examiner that the line preceding the word "complementary" on line 2 of claim 5 (page 16 of the Amendment of January 6, 2003) is actually a "strikethrough" for the comma preceding that word and is not a hyphen that was entered into the claim in the last amendment. Indeed, if the Examiner would turn to pages 6 and 18 of the Amendment of January 6, 2003, the Examiner would readily see that the clean copy of claim 5 does not include a hyphen or the comma that was in the claim prior to the amendment of January 6, 2003. With respect to the Examiner's request for the addition of the article "a" before the word "base" on line 4, applicant has entered the article as suggested by the Examiner.

With respect to the Examiner's continued objection of the term "an RNA" in claim 20, applicant once again traverses this objection. In the prior Amendment, applicant's traversed the Examiner's objection of the term "an RNA" with arguments explaining that the use of the phrase "an RNA" is proper because the article "an" is used before an acronym, such as "RNA," that starts with a consonant but that sounds like it starts with a vowel (i.e., the "R" in the acronym "RNA" sounds like the word 'are,' which starts with a vowel). Applicant respectfully reiterates these prior arguments and provide documentation supporting that the use of the phrase "an RNA" is actually proper in claim 20. Specifically, applicant has attached to the end of this Amendment, an article from the journal *Origins* entitled "Did Life Begin in an RNA World" (Exhibit A) as well as a page from the MIT Newsletter TechTalk entitled "Scientists Ask: Was it Once an RNA World? (Exhibit B); in both of these articles, the phrase "an RNA" is used rather than the phrase "a RNA." Further were the Examiner to conduct a quick Internet search of the terms "a RNA" versus "an RNA," the Examiner would find that the term "a RNA" just yields references to "poly A RNA" whereas the term "an RNA" yields references relating to RNA generally; applicant has submitted the first pages of a search for both terms conducted on the Google search engine to illustrate this point (Exhibit C has the first page of the search for "an RNA" and Exhibit D has the first page of the search for "a RNA"). Further, a review of recently issued patents on the USPTO database shows that the terminology "an RNA" is used over "a RNA" (*see, e.g.*, claim 10 of U.S. Patent No. 6,576,443 and claim 16 of U.S. Patent No. 6,573,369).

In light of the foregoing, applicant respectfully requests withdrawal of the outstanding objections to claims 5 and 20.

CLAIM REJECTIONS - 35 U.S.C. § 112, 2ND PARA.

Claims 1, 2, 5-15, 18-25, 27-31, and 34-39 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner specified objectionable language in claims 1, 2, 5, 18, and 31.

In response to the rejection of claim 1, the claim was amended to clarify that the at least two oligonucleotide probes has one nucleotide capable of base pairing with one nucleotide of at least two sets of two or more nucleotides, said sets having one nucleotide in common and lacking one nucleotide present in the target sequence segment.

In response to the rejection of claim 2, the claim was amended to clarify that each oligonucleotide probe comprises, at a position corresponding to the position of interest, a nucleotide capable of base pairing with any two of the four nucleotides present in the target sequence segment.

In response to the rejection of claim 5, the claim was amended to clarify that the null hybridizing sequence is capable of base pairing with a set of two or more nucleotides at a variable position of the target sequence segment.

In response to the rejection of claim 18, the claim was amended to delete extraneous language.

In response to the rejection of claim 31, the claim was amended to depend from claim 30 rather than claim 15.

In addition to the foregoing, although not rejected, claims 14 and 15 were amended to clarify the recitation relating to the target signal and claim 33 was amended to depend from claim 7 rather than claim 17.

In light of the foregoing amendments and remarks, applicant respectfully requests reconsideration and withdrawal of all indefiniteness rejections.

CLAIM REJECTION – 35 U.S.C. § 102(e)

Claims 1, 6, 18, 19, 23, and 24 stand rejected under 35 U.S.C. § 102(e) as anticipated by Senapathy (U.S. Patent No. 6,521,428). The rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992).

Senapathy teaches a method for sequencing and amplifying nucleic acid templates using a degenerate primer with a fixed sequence region and a random sequence region.

For sequencing, the method of Senapathy provides the following: (a) plurality of first primers, each first primer comprising (i) a region of fixed nucleotide sequence and (ii) a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or interspersed within the region of fixed nucleotide sequence, and then (b) annealing the first plurality of primers to a nucleic template, wherein at least one primer anneals to the template. The annealed first primer is then (c) extended with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments. The nucleotide sequence of a first region of the template is then (d) determined from the series of nucleic acid fragments. Col. 3, lines 30-42. A second primer can be used to determine a second region of the template. Under the method of Senapathy, the first sequenced region and the second sequenced region of the template nucleic acid may be

assembled to form a continguous sequence ("contig"). Col. 3, lines 43-54. Sequence gaps between contigs may be determined by providing a plurality of third primers, each third primer comprising (i) a region of fixed nucleotide sequence and (ii) a region of random nucleotide sequence located 5' to, 3' to, flanking, or within the region of fixed nucleotide sequence and annealing the plurality of third primers to the nucleic acid template, wherein at least one primer from the third plurality anneals to the template near a terminus of one of the first or second contigs. The annealed third primer is then extended with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments. The sequence of the template between the first and second contigs is then determined from the series of nucleic acid fragments. Col. 3, lines 55-67. To sequence an entire length of a target nucleic acid molecule, the methods set forth above are repeated as often as desired. Col. 4, lines 1-3.

For amplification, the method of Senapathy provides a plurality of first primers and second primers, each first and second primer comprising (i) a region of fixed nucleotide sequence and (ii) a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or within the region of fixed nucleotide sequence, wherein the region of the fixed nucleotide sequence of the second plurality of primers is shorter than the region of fixed nucleotide sequence of the first plurality of primers, and then amplifying the nucleic acid template with the first and second plurality of primers, wherein at least one primer from the first and second plurality anneals to the template. Col. 4, lines 4-20.

Senapathy explains that the purpose of the method disclosed therein is to use longer full-length primers for cycle sequencing when little or no information of template DNA is available (col. 2, lines 63-66). Senapathy does not disclose that the procedure entails using fewer probes, all that is disclosed is that longer probes are used.

The present invention differs from Senapathy on at least two grounds.

First, the present invention does not strive to produce longer probes; rather, its aim is to use a smaller number of hybridizing probes for both sequencing and amplification, while obtaining the same amount of information from the hybridization (specification, page 5, lines 21-23). Accordingly, the touchstone of the present invention is not longer probes that are not necessarily fewer in number, but rather fewer probes that are not necessarily longer.

Second, the probes of the present invention do not include a region of fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or within the region of fixed nucleotide sequence. As explained at pages 8-9 of the specification, hybridization between the first probe and the second probe, independently, with a nucleotide at the position of interest occurs only if complementarity exists between a nucleotide at a position of interest and a nucleotide at the

corresponding position of each independent probe (bridging paragraph). Further, hybridization will not occur where there is a single base pair mismatch (specification, page 8, lines 21-24; *see also,* page 15, lines 4-31, which defines the term "complementarity" and explains the mismatch frequency of the present invention). On page 18 of the specification, it is explained why two or more variable positions complicates the statistical analysis of the present invention (first full paragraph, lines 4-20). This analysis contrasts sharply with the statistical analysis of Senapathy (col. 15, line 61 to col. 16, line 16), which supports the hybridization of one or a few mismatches (i.e., 8-10, *see* col. 15, lines 58-59) anywhere on the 5' half of the degenerate primer (col. 15, lines 43-59; Fig. 3). An explanation of how the present invention works in a sequencing context is set forth at page 25, line 7 to page 26, line 9. This explanation shows that unlike Senapathy, where the hybridization is dependent on the fixed nucleotides, the hybridization of the present invention is dependent on the determinate use of degenerate base pairing.

Because Senapathy clearly omits critical elements of the claimed invention, the claimed invention is not anticipated by Senapathy. Accordingly, applicant respectfully requests reconsideration and withdrawal of this rejection.

CLAIM REJECTION – 35 U.S.C. § 103(a)

Claims 21 and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Senapathy as applied above in view of Santamaria et al. This rejection is respectfully traversed.

The Examiner's obviousness rejection is premised on the anticipation of claims 1, 6, 19, 19, 23 and 24 over Senapathy. With respect to the present claims, the Examiner notes that Senapathy does not teach the method therein for genetic analysis, such as allelic analysis as recited in claims 21 and 22. It is the Examiner's position that Santamaria et al. provides the missing teaching because it discloses a sequencing method used for genetic (i.e., allelic) analysis.

The foregoing discussion explains why Senapathy does not anticipate the claimed invention. Because the Examiner's obviousness analysis is premised on the anticipation of claim 1 over Senapathy, it follows that if Senapathy does not anticipate the claimed invention, then the teachings of Santamaria et al. will not render claims 21 and 22 obvious.

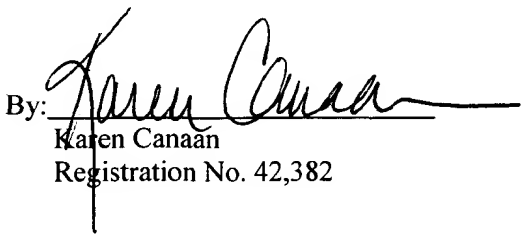
In light of the foregoing, applicant submits that this rejection is rendered moot in light of the arguments set forth herein distinguishing the claimed invention over Senapathy. Accordingly, applicant respectfully requests reversal of this rejection.

CONCLUSION

Because all of the claim objections and claim rejections set forth by the Examiner have been addressed and resolved with this Amendment, applicant respectfully requests withdrawal of all claim objections and rejections and passage of this application to allowance.

The Examiner is welcome to contact the undersigned attorney at 650-330-4913 to discuss any issues regarding this Amendment.

Respectfully submitted,

By: 
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DID LIFE BEGIN IN AN "RNA WORLD"?

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Origins 20(1):45-52 (1993).
Related page — | REACTION |

WHAT THIS ARTICLE IS ABOUT

Recent discoveries of catalytic activity by RNA has stimulated speculation that life may have originated naturalistically through the formation and evolution of RNA molecules. This "RNA World" hypothesis has numerous shortcomings. RNA is difficult to produce chemically. The materials required for its production would not be present on a prebiotic earth. The "RNA World" scenario is not a plausible explanation for the origin of life.

Explaining the origin of life has remained one of the most bothersome problems for those espousing the view that nature can only be understood within a naturalistic philosophy. For many years the major focus of attention has been on scenarios involving the evolution of proteins. Two historical factors contributed to the emphasis on proteins. One of these was that when scientific investigation of the origin of life was beginning, the role of nucleic acids in heredity had not been established. It was reasonable at that time to suppose that proteins might be responsible for heredity. The other factor was the production of amino acids in simulated prebiotic reactions (Miller 1953). This experimental result seemed to promise the possibility of success in explaining the origin of life, even though nucleic acids were known at the time to be important also in heredity.

For many years there has been a general dissatisfaction with the protein hypothesis of the origin of life. Proteins cannot replicate themselves, making them unsuitable as a starting point for the development of life. However, there seemed to be no naturalistic alternative available until recently. This newer hypothesis has been dubbed the "RNA World" (Gilbert 1986). The basis for this model is the discovery that certain RNA molecules have catalytic properties. Since RNA also serves as a carrier of information, it seemed reasonable to suggest that ancient RNA molecules might have acted as a starting point for the origin of life. The "RNA World" hypothesis for the origin of life seems a significant improvement over the protein hypothesis, and has been the subject of considerable discussion. The plausibility of that hypothesis is examined in this paper.

Importance of RNA. RNA is present in all living cells, and has a variety of uses that are central to the requirements for life. RNA plays an important role in cellular processes, especially in protein manufacture. Molecules of messenger RNA (mRNA) contain the information needed to specify the proper amino acid sequences of proteins. The mRNA acts as a template for the assembly of protein molecules. Ribosomal-RNA (rRNA) sequences participate in reading the message on the messenger RNA and joining the amino acids together in a chain. Transfer-RNA (tRNA) molecules arrange the amino acids in proper sequence. RNA molecules also have catalytic properties (reviewed by Lamond and Gibson 1990). Messenger RNA molecules often contain non-coding sequences, known as introns. These introns are removed before the message is translated into a protein. The mechanism of removal is

self-splicing by the intron, in which RNA acts as a catalyst. Ribosomal RNA can catalyze the formation of peptide bonds between amino acids in the production of a protein (Noller, Hoffarth, and Zimniak 1992). Several other examples of RNA catalysis are known. The discovery of RNA catalysis has stimulated the idea that life may have originated with RNA molecules.

Since RNA can act both as a template and as a catalyst, it might be possible that an RNA molecule, acting as a "ribozyme," could make copies of itself without the need for other kinds of molecules. One strand of a two-stranded RNA sequence could act as the template while the complementary strand could act as an enzyme, catalyzing replication of the RNA sequence (see Cech 1989). Once this step was achieved, variations in sequence would occur which could compete with each other, leading to more complex arrangements. Hypothetically, life might eventually arise. Doudna and Szostak (1989) succeeded in constructing an RNA which would make copies of a template sequence. If an RNA molecule could also make copies of its own sequence, it would be able to replicate both RNA strands, and the cycle could be repeated indefinitely. Another alternative is for two or more different RNA strands to participate in reaction cycles that catalyze each other, forming systems known as hypercycles (Eigen et al. 1981).

Reasons for Thinking RNA Preceded DNA. RNA is thought to have preceded DNA in the origin of life (Lamond and Gibson 1990). One reason for this suggestion is that RNA replication is much simpler than DNA replication, for it involves fewer types of molecules. Another reason is that cells produce DNA nucleotides from RNA nucleotides. A third reason is that RNA primers are required for initiation of DNA replication, whereas RNA polymerases (enzymes that produce copies of RNA sequences) do not require a primer.

SOURCE OF BUILDING BLOCKS FOR RNA NUCLEOTIDES

Nucleic acids are composed of three kinds of building blocks: a sugar, a phosphate, and an organic base. The base may he either a purine or a pyrimidine. These three parts combine to form a nucleotide, which is the basic building block of nucleic acids. In the case of RNA, the sugar is ribose, the purines are adenine and guanine, and the pyrimidines are cytosine and uracil. The production of these building blocks is the first step in the proposed "RNA World."

Production of Ribose. Ribose, a five-carbon sugar, is an integral component of RNA. Ribose can be produced by the formose reaction, in which polymerization of formaldehyde is catalyzed by a base. This reaction has been proposed as the most likely prebiotic source of ribose. It requires formaldehyde, which is thought to have been present on a prebiotic earth (Kasting 1993).

Experimental Support. It seems plausible that formaldehyde might be produced in reactions among gases in a prebiotic atmosphere that is not strongly reducing (Pinto et al. 1980). Formaldehyde can also be produced by photochemical oxidation of methane. However, at present methane is produced largely as a result of biological activity, and it is unlikely to have been present in significant quantities on a prebiotic earth. Extraterrestrial sources of formaldehyde have also been proposed. Comets and interplanetary dust particles (IDPs) are another possible source of formaldehyde. Comets are said to contain about 25% organic matter, of which 4% may be formaldehyde (Chyba et al. 1990). Production of ribose from formaldehyde has been demonstrated in the laboratory.

Problems with Ribose Production. Although it is conceivable that some formaldehyde could be produced in the atmosphere of a prebiotic world, it is unlikely that significant quantities would be present. There is some doubt that formaldehyde or other organic compounds on comets would survive a

collision with the earth. However, even if formaldehyde were present, this does not mean ribose would be produced. Ribose is a very minor product in a complex mixture of compounds produced in the formose reaction, and is rapidly destroyed under the reaction conditions (Shapiro 1988). Furthermore, ribose is considered to be unstable on a geologic time scale, and would probably disappear in a few hundred years (Joyce et al. 1987). A carbon dioxide atmosphere would further inhibit the desired reactions. Carbon dioxide from the atmosphere would dissolve in the ocean, producing acidic conditions that would hydrolyze sugar molecules.

Sugars may be produced in other reactions, but ribose is not one of the products. UV irradiation of formaldehyde produces pentaerythritol, and no ribose (Schwartz and de Graaf 1993). Sugars may also be formed from glyceraldehyde in the presence of iron (III) hydroxide (Weber 1992). However, only hexoses (6-carbon sugars) are formed. There seems to be no plausible prebiotic source for ribose. Additional problems of chirality (mirror image), chemical interference and decomposition of sugar make the production of ribose a major problem for a naturalistic explanation of the origin of life.

Production of Purine and Pyrimidine Bases. It is believed that cyanide present in the primitive atmosphere might be a precursor in the production of purines, pyrimidines and amino acids.

Experimental Support. Maurel states (1992) that purines can be obtained from cyanide in water. The source of cyanide is said to be a major problem in the "RNA World" hypothesis (Kasting 1993). However, hydrogen cyanide is reported to constitute about 7% of the organic matter of comets (Chyba et al. 1990), so perhaps the presence of cyanide cannot be ruled out.

Problems with Purine and Pyrimidine Bases. Kasting (1993) has pointed out that there is no plausible way of forming cyanide in a prebiotic atmosphere. According to De Duve and Miller (1991), the experimental conditions under which purines can be produced from cyanide are greatly contrived. The presence of a carbon dioxide atmosphere would inhibit the production of purines from cyanide (Chyba et al. 1990). Any purines or pyrimidines present would be hydrolyzed in the ocean made acidic by the presence of carbon dioxide. Pyrimidines are, for all practical purposes, not formed in postulated prebiotic conditions (Maurel 1992).

Problems with Phosphate. Phosphate is required to join the base-sugar pairs (nucleosides) of nucleic acids. Phosphorus is much less abundant than the other elements found in RNA. Yamagata et al. have reported (1991) the presence of polyphosphates (chains of phosphate groups) in volcanic emissions, and has suggested volcanos as a source of the phosphate required for the origin of life. One difficulty with this proposal is that polyphosphates would hydrolyze in water to form insoluble phosphates, which would precipitate to the ocean floor. There seems to be no other possible source of phosphates. An ocean associated with a carbon dioxide atmosphere will be so acidic that phosphate would not be available for chemical reactions.

FROM SUGARS, PHOSPHATES AND BASES TO NUCLEOTIDES

Problems of Assembling Nucleotides. Although the prebiotic production of the building blocks of RNA is highly implausible, there are additional problems involved in combining these units into ribonucleotides. One problem is the production of a mixture of sugars with the ribose. Extra sugars would inhibit RNA synthesis (Horgan 1991). Purines will unite with ribose when heated, but the products include many different sugar-base combinations (nucleosides) and their analogues, and only a small percentage of useful nucleosides (those with beta bonding) (Joyce et al. 1987). Pyrimidines; do not form any useful nucleosides under similar conditions. Under realistic prebiotic conditions, no

nucleotides would be formed (Cairns-Smith 1985).

FROM NUCLEOTIDES TO RNA

Problems in Combining Nucleotides to Form RNA. A further problem with the "RNA World" hypothesis is that ribonucleotides may bond in different ways, only one of which is appropriate for RNA (Ferris and Ertem 1992). Ribonucleotides can occur in D- and L- forms. Only the D forms are useful in living systems, but both forms would be present in any prebiotic mixture. The presence of L-ribonucleotides strongly inhibits the addition of D-ribonucleotides on a template (Joyce et al.1987). The problem of chirality is so severe that a chirally pure medium seems a necessity for RNA to be produced (Avetisov et al. 1991).

FROM RNA TO LIFE

Even if RNA were produced, there would still be no life. The importance of RNA to the origin of life is based on the conjecture that it could act both as a source of information and as a catalyst to use that information. But RNA must be folded to act as a catalyst, and must be unfolded to act as a source of information (Green and Szostak 1992). In addition, RNA is not a good self-replicator (Horgan 1991). Even if self-replicating RNA should arise, selection would favor greatest ease in replication, and information content would probably be selected against (Wicken 1985). RNA breaks down rapidly in water (Day 1991), especially hot water, or in the presence of divalent cations (Pace 1991). Thus every step in the production of RNA is highly implausible under the proposed prebiotic conditions. Even if RNA were produced, it could not survive nor could it form the basis for a naturalistic origin of life. Some other mechanism must be sought to explain the origin of life.

CONCLUSION

Naturalistic models for the origin of life generally begin with the production of small molecules such as sugars or amino acids, which then combine to form larger molecules such as proteins or nucleic acids. These large molecules must then become organized into cellular structures that are somehow interrelated in complex ways and under non-equilibrium conditions. The "RNA World" hypothesis for the origin of life requires implausible events at each step in the sequence outlined. Small molecules are highly unlikely to have been available in any plausible model of a primordial earth. Even if small molecules were present, they would be highly unlikely to produce the large protein and nucleic-acid molecules useful for life. Even if the large molecules were present, there is no known mechanism whereby they might be organized into functional cellular or subcellular units. The "RNA World" hypothesis suffers from many of the same problems as the protein hypothesis, and has additional problems of its own. Considering the conditions necessary for the establishment of life, it appears that the most plausible explanation for the origin of life is an intelligent creator.

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TechTalk

Published by the MIT News Office at the Massachusetts Institute of Technology, Cambridge, Mass.

WEDNESDAY, JULY 15, 1998

Scientists ask: was it once an RNA world?

For scientists, the question isn't just how life began. The real question might be: How many times did life begin?

In the early years of Earth's existence, there were so many cataclysmic events like meteor impacts that the oceans would repeatedly boil away and nascent life forms would be wiped out. So the fact that life seems to have started 3.5 billion years ago -- relatively soon after the planet was formed -- indicates that life may have started several times before it had enough time to evolve. Meanwhile, the chances of having the right components fall together in the right configuration seem unbelievably small.

David Bartel, assistant professor of biology, explained to visiting teachers that biologists have wrestled with a chicken-and-egg problem. What was around first: protein, the building blocks of living matter, or nucleic acid, the building blocks of genetic material?

RNA, formed on a DNA template, plays a crucial role in protein synthesis and enables genetic material to replicate itself.

Although there's no question that it's now a protein world, was it an RNA world way back when? "It's the molecular biologist's dream -- and the chemist's nightmare -- that we can deduce that RNA played more of a role than it does today," Professor Bartel said.

To answer questions like these, he and his colleagues are engineering a ribosome to carry out slow, simple reactions in the hope that it will provide clues to whether and how RNA nucleotides can join to another piece of RNA to form different sequences and increase its length. A ribosome is a small cell component in very simple organisms where the sequence of amino acids in a polypeptide chain is specified.

"We're having a lot of fun seeing what RNA can do," Professor Bartel said. "We're using the same techniques that exist in nature to find out about this ultimate evolutionary experiment."

Deborah Halber

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